

REMARKS

The Office Action of April 29, 2008, and the prior art relied upon therein have been carefully reviewed. The claims in the application are now independent claim 10 and dependent claims 4, 5 and 13-20, and these claims define patentable subject matter for the reason pointed out below. Favorable reconsideration and allowance are respectfully urged.

Acknowledgement by the PTO of the receipt of applicants' papers filed under Section 119 is noted.

New claims 13-20 have been added. Support for claim 13 is implicit from the entirety of the specification including the working examples which show that the substance of the present invention can be administered to a mammal. Claim 16, which depends from claim 13, is supported by the sentence spanning pages 9 and 10.

Claim 14 is supported for example by the text at page 15, lines 17-22 of the specification. Claim 20 which depends therefrom is supported at page 15, line 24.

Claim 15 is supported by the text at page 15, lines 7-16.

Claim 17 is supported in applicants' specification at page 9, last line. Claim 18 is supported at page 12, line 27 of applicants' specification, and claim 19 is supported at page 10 line 4 of applicants' specification.

These claims are patentable for **at least** the reason that they depend from and incorporate the subject matter of claim 10 from which they directly or ultimately depend.

Claims 2-5 and 10 have been rejected under the first paragraph of Section 112 as lacking enablement for the claimed subject matter. The rejection is respectfully traversed.

Claims 2 and 3 have now been deleted without prejudice to applicants' right to pursue those or similar claims in a continuing application if applicants choose to do so; therefore, this rejection need not be addressed at the present time with respect to claims 2 and 3.

The rejection asserts that the specification does not reasonably provide enablement to the person skilled in the art for a method of recruiting fibroblast in general (claim 10) or to any wounded site (claim 2) in any animal other than mice. By the above amendments to claim 10, it is now made explicit that the fibroblast are recruited to the heart, and that thus addresses the issue of the site.

As regards the examples which use mice as the test animals, the rejection indicates that it is unclear as to whether or not the model used in the present application is an art-accepted model. However, applicants respectfully believe and strongly maintain that the mouse is an art-accepted model, and applicants present herewith evidence in support of applicants' position.

As shown in the following documents, a mouse model of myocardial infarction produced by ligating the left anterior descending coronary anterior is widely used in the art. Therefore, the model used in the present invention is an art-accepted model.

Reference 1: Yang et al, Experimental Physiology. 87.5. pp.547-555 (2002);

Reference 2: Eberli et al, Journal of Molecular and Cellular Cardiology. 1443-1447 (1998); and

Reference 3: Fukuhara et al, The Journal of Heart and Lung Transplantation. Vol.24. No.1. pp.67-72 (2005).

As will be clear from the foregoing, the model used in the instant invention has been used by many research scientists in the present art. Reference 1 states that "Animal models of cardiovascular disease have frequently been used to study pathophysiological mechanisms and test various strategies." It is considered from this that it should be

clear that the findings obtained from the model used can be applied to other mammals.

Further, in accordance with the present invention, fibroblasts are caused to migrate from bone marrow by administration of G-CSF. Please refer to page 3, lines 26-28 of the specification (In the present invention, G-CSF can be administered after myocardial infarction so as to induce migration of fibroblasts from the bone marrow). It is considered that since fibroblasts in mice can be caused to migrate, fibroblasts in a human being (who has the same general type of bone marrow as mice) can also be expected to migrate.

Withdrawal of the rejection is in order and is respectfully requested.

Claims 2-5 and 10 have been rejected under the second paragraph of Section 112. The rejection is respectfully traversed.

The specification of the present application discloses that even when G-CSF is administered subcutaneously, fibroblasts can be recruited to the heart (please refer to Examples 1-3). In general, it is known that a medicament administered by a subcutaneous injection can penetrate from the subcutis to the blood, even though the concentration of

the medicament is low at the action site. It is confirmed by the working examples of the present application (Examples 1-3) that even if the concentration of a medicament is low in an action site as in the case of a subcutaneous injection, the recruitment of fibroblasts can be achieved as long as G-CSF reaches the blood.

G-CSF reaches the blood by a method of administration other than an injection such as oral administration and percutaneous administration, though there is a difference in the blood level of G-CSF among subcutaneous, oral and percutaneous administrations. Therefore, it is evident that as long as a method wherein G-CSF can reach blood is used, the advantageous results of the present invention can be achieved even if the method of administration of G-CSF is not limited. Please refer to the statement "The substances of the present invention for fibroblast recruitment or other purpose may be administered in a dosage form injections (e. g., subcutaneous, intracutaneous not limited by the route of administration or dosage form, etc." (page 15, lines 7-16 of the specification).

A claim is not indefinite simply because it is broad. Applicants' claims are narrow in some respects and broad in others, and such claims are properly broad insofar as concerns the method and locus of administration. As those

skilled in the present art are highly skilled individuals, and would fully understand applicants' claims, the claims are not indefinite.

Withdrawal of the rejection is in order and is respectfully requested.

Claims 2-5 and 10 have been rejected under Section 102 as anticipated by Orlic et al, Reference U (Orlic). This rejection is respectfully traversed.

First, although this is not applicants' main point, the rejection is clearly inconsistent with the restriction requirement.

By requiring restriction, the PTO held that the elected invention I was patentably distinct from inventions II and III relating respectively to ingrafting fibroblast in a heart and wound healing. The criteria for restriction are the same as those for determining obviousness. In other words, when something is "patentably distinct" from something else, it is patentable over that from which it is patentably distinct. Respectfully, it is improper for the PTO to use a double standard.

Perhaps more importantly, however, Orlic does not show or describe the claimed subject matter because Orlic shows an advantageous effect caused only by the combined use

of both stem cell factor (SCF) and G-CSF. In other words, Orlic does not at all disclose clearly an advantageous effect which is characteristic of each of SCF and G-CSF. Even if Orlic is carefully perused, it is quite unclear whether the characteristic property of G-CSF itself against myocardial infarction is produced even inherently.

Further, Orlic states to the effect that SCF could be responsible for recruiting bone marrow cells (please refer to page 10349, left column, lines 11-17). Therefore, it cannot be concluded that Orlic discloses and thus anticipates that the use of G-CSF by itself produces the advantageous effect of recruiting fibroblasts into myocardial infarct lesions.

The inventors of the present application first provided a method of recruiting fibroblasts in a heart, for example, myocardial infarct lesions by using G-CSF only. This method was provided for the first time based on the finding that G-CSF administration induced migration of various stem cell-derived cells such as fibroblasts (connective tissue) from the bone marrow into infarct lesions and allowed regeneration of the infarct regions (please refer to "... allowed regeneration of the infarct lesions." appearing on page 3, line 15 of the specification). Orlic does not teach or suggest this finding or the claimed method.

As Orlic does not anticipate the claimed method, withdrawal of the rejection is in order and is respectfully requested.

Claims 2-5 and 10 have also been rejected under Section 102 as anticipated by Mehta et al USP 7,220,407 (Mehta). This rejection is respectfully traversed.

Again, the examiner required restriction between the elected subject matter, namely recruiting fibroblast, and non-elected and withdrawn wound healing of claim 12, holding that these are patentably distinct from one another, i.e. patentable over one another. Mehta does not at all disclose that G-CSF recruits fibroblast (applicants' elected subject matter).

In addition, what Mehta really discloses and teaches involves G-CSF therapy **as an adjunct** to reperfusion therapy such as a bypass surgery (please refer to the title of the invention, ABSTRACT and all claims, particularly claim 9). Thus, the invention, disclosure and teachings of Mehta are quite different from the present invention which relates to a method of recruiting fibroblasts into myocardial infarct lesions to regenerate the lesions.

It is the inventors of the present application who, for the first time, disclosed a method of recruiting

fibroblasts into a heart, for example, myocardial infarct lesions by using G-CSF only. Mehta neither teaches nor suggests this method. Furthermore, since the present invention can provide fibroblasts (connective tissue), the following surprising results are produced: myocardial infarct lesions are regenerated (please refer to "... allowed regeneration of the infarct lesions." appearing on page 3, line 15 of the specification) and a healed tissue that is much stronger can be formed (please refer to "... a healed tissue that is much stronger." appearing on page 4, lines 10-11 of the specification).

Withdrawal of the rejection is in order and is respectfully requested.

Claims 2-5 and 10 have also been rejected as anticipated by Michal et al USP 7,294,334 (Michal). This rejection is respectfully traversed.

Like the other citations applied against applicants' claims, Michal does not disclose and does not teach the use of G-CSF by itself, or include the faintest implication that G-CSF by itself can carry out any useful function.

Michal exhaustively discloses methods, devices, kits and compositions to treat myocardial infarction. Indeed, as pointed out by the Examiner, Michal teaches that treatment

agents, including G-CSF, can be used together to modify the replacement cell population (please refer to ABSTRACT and column 25, lines 5-21). However, the term G-CSF merely appears only once in the 11th to 12th lines of column 25, and Michal does not describe the advantageous effect produced by the use of G-CSF in treating myocardial infarction (please refer to the examples of Michal). Therefore, the present invention, completed based on the finding that G-CSF has an advantageous effect of recruiting fibroblasts, is not at all anticipated by Michal.

Withdrawal of the rejection is in order and is respectfully requested.

Claims 2-5 and 10 have been provisionally rejected on the basis of obviousness-type double patenting over claims 1 and 2 of a co-pending application published under 2006/0104942; and over "at least claims 1 and 3" of a co-pending U.S patent application published under the number 2004/0019184. These provisional rejections are respectfully traversed.

First, they are traversed because they are premature. There can be no double patenting until there are patent claims, and at this stage there are no such patent claims.

Second, these rejections are respectfully traversed because they are inconsistent with the restriction requirement as pointed out above. It is simply unfair for the PTO to apply the same criteria in two completely different and opposite ways. As pointed out above, restriction is based on patentable distinctness, and patentable distinctness is based on the criteria of Section 103, obviousness. Claims cannot be non-obvious from one another in one context, and obvious from one another in another context. It is simply wrong and unfair.

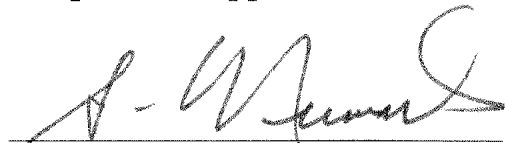
Withdrawal of the provisional double patenting rejections is respectfully requested.

Applicants believe that all issues raised in the Official Action have been addressed above. Favorable reconsideration and early formal allowance are respectfully requested.

Respectfully submitted,

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